REMARKS

The Invention

The invention is generally directed to novel methods for identifying polypeptides that modulate gene expression from a promoter in a mammalian cell. These methods make use of the expression of anti-cell death proteins in the mammalian host cell to improve screening efficiency by reducing cellular toxicity resulting from the screening procedure.

The Office Action

Claims 1-4, 7, 9-12, 14, 15, 19, 21-23, and 45-49 are pending. Claims 1, 3, 7, 9-12, 14, 15, and 45-49 are withdrawn as being directed to non-elected subject matter. The remaining claims stand rejected as being indefinite and as being obvious over Korsmeyer (U.S. Patent No. 5,834,209) in view of Kamb (WO98/36097). Each of these rejections is addressed in turn below.

Summary of the Amendments

Support for the amendments is found throughout the specification as filed. No new matter has been added.

Restriction Requirement

The Office asserts that amended claims 1, 3, 7, 9-12, 14, and 15, and newly filed claims 45-49, are directed to an invention other than the invention that was subject to an action on the merits. On this basis, the Office has withdrawn claims 1, 3, 7, 9-12, 14, 15, and 45-49 from consideration. For the reasons provided below, applicants respectfully submit that this withdrawal was in error, and request (i) reinstatement and examination of the withdrawn claims, and (ii) withdrawal of finality.

The withdrawal of claim 1, 3, 7, 9-12, 14, 15, and 45-49 was improper

Applicants first submit that the withdrawal of claim 1, 3, 7, 9-12, 14, 15, and 45-49 as being directed to a nonelected invention was improper, and request reconsideration. As discussed below, these claims are drawn to the elected invention, as set forth by the Office, and thus should have been examined on the merits.

A restriction requirement was mailed in the present case on March 5, 2003. In this restriction requirement, the Office identified thirteen groups. In reply, applicants elected Group I (claims 1-4, 7-16, and 19-23), drawn to "a method of identifying polypeptides which increase or decrease gene expression from a promoter."

A first Office action issued on July 29, 2003, reporting examination of the claims of Group I as filed. In their reply of October 29, 2003, applicants amended claims 1 and 3 and added new claims 45-49. Each of these claims is directed to the elected group, namely a method of identifying polypeptides that increase or decrease gene expression

from a promoter.[1] As these claims are drawn to the elected invention of Group I, these claims should not have been withdrawn but rather examined on the merits. Such action is respectfully requested.

Finality should be withdrawn

Applicants also respectfully request that the Office withdraw finality of the most recent Office action. As is discussed above, the withdrawal of claims 1, 3, 7, 9-12, 14, 15, and 45-49 was improper; these claims should have been examined on the merits. Because these claims were withdrawn, they were not examined in the present Office action. If finality of this most recent Office action is maintained, applicants will be deprived of having claims 1, 3, 7, 9-12, 14, 15, and 45-49 examined in the instant application. Applicants submit that, because of the improper withdrawal of claims 1, 3, 7, 9-12, 14, 15, and 45-49, the final rejection of the remaining claims is premature, and reconsideration and withdrawal of finality is respectfully requested.

[1] This is demonstrated by examining the preamble of the four withdrawn independent claims: claim 1 is directed to "[a] method for identifying a library of polypeptides which includes one or more polypeptides that increase gene expression from a promoter"; claim 3 is directed to "[a] method for identifying a library of polypeptides which includes one or more polypeptides that decrease gene expression from a promoter"; claim 45 is directed to "[a] method for identifying a polypeptide which increases gene expression from a promoter"; claim 46 is directed to "[a] method for identifying a polypeptide which decreases gene expression from a promoter."

Rejections under 35 U.S.C. § 112, second paragraph

Claims 2, 4, 19, and 21-23 are rejected as being indefinite. Each of these rejections is addressed in turn below.

Claims 2 and 4

Claims 2 and 4 are rejected as being indefinite. The crux of the rejection appears to center on the claim term "less complexity." Applicants respectfully traverse this rejection.

Step (c) of each of claims 2 and 4 recites that the library of step (a) is divided into two or more libraries having "less complexity" than that of the parent library. One of ordinary skill in the art of molecular biology would understand complexity to mean the number of different molecules in the library. This same person would also understand that a library having "less complexity" is one having fewer numbers of different molecules. For example, a library of one million DNA molecules suspended in 40 mL of buffer may be divided into two aliquots of 20 mL each. Each of these aliquots is a library having less complexity that the parent library. It would be readily apparent to a practitioner what activities are and are not encompassed by step (c) of each of claims 2 and 4, and, for this reason, reconsideration and withdrawal of this rejection is respectfully requested.

Claims 2 and 4 are further rejected as being indefinite for (i) failing to recite an essential step; and (ii) being contradictory. Applicants have addressed these rejections by amendment of claims 2 and 4, and these rejections may also be withdrawn.

Claims 19 and 21-23

Claims 19 and 21-23 stand rejected for depending from withdrawn claims 1 and 3. As discussed above, it is applicants' position that the withdrawal of claims 1 and 3 was improper, as these claims are drawn to the elected invention. Reinstatement of claims 1 and 3, as requested by applicants, would obviate the present rejection of claims 19 and 21-23.

Rejections under 35 U.S.C. § 103(a)

Claims 2, 4, 19, and 21-23 are rejected as being obvious over Korsmeyer (U.S. Patent No. 5,834,209) in view of Kamb (WO98/36097). This rejection is respectfully traversed.

In their previous reply, applicants argued that Korsmeyer describes a yeast two-hybrid screen in which a library of mammalian proteins fused to a transactivation domain is tested for the ability to bind to the anti-cell death protein Bcl-2 fused to a DNA binding domain. Intermolecular binding between the two fusion proteins leads to transcriptional activation of a reporter gene and identification of the protein capable of binding Bcl-2. Applicants concluded that there would not have been a reasonable expectation that

Korsmeyer's method, used solely in yeast cells, would work in mammalian cells, as is required in the pending claims.

In the present Office action, the Office points to a second assay described by Korsmeyer. This assay is to identify therapeutic agents that block the binding of Bcl-2 or a related protein to the pro-apoptotic Bad protein. The sum of the teachings is provided below:

> In one embodiment, candidate therapeutic agents are identified by their ability to block the binding of a Bad polypeptide to a bcl-x_L polypeptide under binding conditions. The Bad polypeptide preferably comprises the Bad BH1 and BH2 domains, and often is a full-length mature Bad protein. The bcl-x_L polypeptide preferably comprises the bcl-x_L BH1 and BH2 domains, and often is a full-length mature human bcl-x_L protein. Compositions for identifying candidate therapeutic agents typically comprise: (1) a Bad polypeptide capable of binding to a Bad-interacting polypeptide (e.g., bcl-x_L, bcl-2), (2) a Bad-interacting polypeptide (e.g., bcl-x_L, bcl-2), (3) aqueous binding conditions (e.g., physiological conditions), and optionally (4) a host cell (e.g., a yeast cell, mammalian cell, bacterial cell), and optionally (5) a reporter polynucleotide, and optionally (6) a medium to support growth or maintenance of a host cell; an agent is typically added to such a composition for evaluation.

(Korsmeyer; column 7, lines 10-17). The Office concludes that "Korsmeyer does not only teach two-hybrid assays but also positively teaches assays in mammalian cell [sic]."[2]

Applicants note that, while Korsmeyer teaches assays in mammalian cells, Korsmeyer does not teach <u>two-hybrid</u> assays in mammalian cells. There is nothing in the foregoing passage that contradicts applicants' previously asserted position, repeated

[2] The Office also cites col.5, lines 38-40, as supporting its position that Korsmeyer teaches assays in mammalian cells. This passage, however, merely states that bcl-x_L and bcl-2 interact *in vivo*, and has no bearing on the patentability of the pending claims.

above, that there would have been no reasonable expectation that Korsmeyer's two-hybrid library screening could be successfully employed in Kamb's mammalian cells.

Apart from being capable of being performed in mammalian cells, the second Korsmeyer assay described above has no commonality with the claimed method. For example, claim 2 recites contacting a library of polypeptides with a mammalian cell; the Korsmeyer passage mentions no such library. Claim 2 also requires that the mammalian cell express a recombinant anti-cell death gene; the Korsmeyer passage refers to an anti-cell death protein, but not an anti-cell death gene. Claim 2 further recites that the reporter gene is operably linked to a promoter; the Korsmeyer passage mentions no such promoter. While applicants have used claim 2 for exemplary purposes, the same differences are found in claim 4, the other examined independent claim.

In sum, Korsmeyer describes two assays—a yeast two-hybrid assay and a second interaction assay to identify agents that interfere with protein-protein interactions. For the reasons discussed above, neither assay alone, in combination with the teachings of Kamb, is sufficient to support an obviousness rejection.

To support its obviousness rejection, the Office does what Korsmeyer does not—it links the library-based yeast two-hybrid library screening with the assay to identify agents that interfere with protein-protein interactions. Quite simply, Korsmeyer does not teach or suggest using mammalian cells in polypeptide library screening.

For all of the foregoing reasons, reconsideration and withdrawal of this rejection is respectfully requested.

Conclusion

Applicants submit that the claims are now in condition for allowance, and such action is respectfully requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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